UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/822,860	04/13/2004	Koichi Matsuzaki	040176	2658

23850 7590 12/14/2006

ARMSTRONG, KRATZ, QUINTOS, HANSON & BROOKS, LLP
1725 K STREET, NW
SUITE 1000
WASHINGTON, DC 20006

EXAMINER	
REDDIG, PETER J	
ART UNIT	**PAPER NUMBER**
1642	

DATE MAILED: 12/14/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/822,860	MATSUZAKI ET AL.	
	Examiner	Art Unit	
	Peter J. Reddig	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *31 October 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-12* is/are pending in the application.

4a) Of the above claim(s) *6-12* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5* is/are rejected.

7)☒ Claim(s) *1* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☒ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *4/13/04 6/7/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *Appendix 1*.

DETAILED ACTION

1. The Election filed October 31, 2006 in response to the Office Action of September 6, 2006 is acknowledged and has been entered.

2. Applicant's election with traverse of Group II, claims 1-5, as drawn to a polyclonal antibody specific for a phosphorylated linker region in Smad3 is acknowledged.

3. Regarding the restriction between Group II and Groups I and III

Applicants argue that in Groups I to III, the Examiner is restricting within each claim between the three cases of the target for the antibody (i.e., Smad2, Smad3 and both Smad2 and Smad3). Applicants argue that this is a restriction between alternatives, and is analogous to restriction within a Markush group. Applicants argue that the present case is, in effect, a Markush group with only three members (as defined by the Examiner), and, in fact, requires search only of the Smad2 and Smad3 cases, since the search for the case of both Smad2 and Smad3 would be included in the searches for Smad2 and Smad3. Applicants argue that the search can be made without serious burden, and that all of Groups I, II and III should be examined.

Applicants' arguments have been carefully considered and have been found persuasive because isolated Smad2 and Smad3 protein phosphorylated in the linker region are found in the prior art and thus Groups I-III will be rejoined.

4. Regarding the restriction between Group II and Groups IV to XIX

Applicants argue that the search for the polyclonal antibodies of Groups I to III would inherently encompass a search for methods of use of these polyclonal antibodies, and that the additional search burden is therefore negligible. Applicants argue that if the polyclonal

antibodies of Groups I to III are found to be not anticipated and not obvious, any method using these specific polyclonal antibodies would also be not anticipated and not obvious.

Applicants' argument has been carefully considered, but have not found persuasive. The methods of Groups IV to XIX have additional steps and limitations, in addition to the use of the polyclonal antibodies, which must be searched and examined for the determination of patentability. Thus, the search of these groups is not coextensive. Furthermore, there would be a serious burden on the examiner if restriction is not required because the inventions have acquired a separate status in the art in view of their different classification and because the inventions of Groups I to III and Groups IV to XIX are independent or distinct for the reasons given above and stated in the restriction requirement of September 6, 2006.

5. Regarding the restriction between Groups VIII to XIII

Applicants argue that the preamble of claim 11 recites a single method that is for assessing the efficacy of fibrosis stimulating signal and assessing the efficacy of the molecular targeting therapy for hepatic fibrosis. Applicants argue that there is no difference in the steps of Claim 11 corresponding to these two purposes. Applicants argue that the stated restriction, which is based only on the wording of the preamble, is improper.

Applicants' arguments have been considered and found persuasive, in part. The Groups will be rejoined as drawn to a method for assessing the activity of fibrosis stimulating signal in hepatic fibrosis and the efficacy of the molecular targeting therapy for hepatic-fibrosis, but will remain restricted to three Groups of methods using antibodies specific for the phosphorylated linker region in Smad2, Smad3, or Smad2 and Smad3 because the search for the distinct

antibodies to Smad2, Smad3, or Smad2 and Smad3 and their relation to the corresponding method is not coextensive.

The issues remain the same for the reasons set forth previously and above, thus the restriction requirement is deemed to be proper and is therefore made FINAL.

6. Claims 1-12 are pending.

7. Claims 6-12 have been withdrawn from further consideration by the examiner under 37 CFR 1.142(b) as being drawn to non-elected inventions.

8. Claims 1-5 are currently under consideration.

Priority

9. Acknowledgment is made of applicant's claim for foreign priority based on an application filed in Japan on October 9, 2003, No. 2003-351259. It is noted, however, that applicant has not filed a certified copy of the Japanese patent application No.2003-351259 as required by 35 U.S.C. 119(b).

Thus, it is noted that, in the absence of the Japanese patent application, examiner has established a priority date for the instant application, 10/822,860, of April 13, 2004 because the priority of the instantly claimed invention is based on the Japanese patent application No.2003-351259. If applicant disagrees with any rejection set forth in this action based on examiner's establishment of a priority date, April 13, 2004, for the instantly claimed application serial number 10/822,860, applicant is invited to submit a certified copy with a translation of the priority document and to point to, page and line where support can be found establishing an earlier priority date. If applicant chooses to file a translation, then the translation must be filed together with a statement that the translation of the certified copy is accurate, see MPEP 201.15.

Specification

10. The disclosure is objected to because of the following informalities: The sentence bridging pages 3 and 4, "The MH1 domain and the MH2 domain are linked together in the region called linker region with low homology," is unclear.

Appropriate correction is required.

11. The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed.

Claims

12. Claim 1 is objected to because of the following informalities: The claim is missing an article, a or the, at the beginning of the claim.

Appropriate correction is required.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

13. Claim 1 is rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter. Claim 1, as written, does not sufficiently distinguish over polyclonal antibodies specific for a phosphorylated linker region in Smad2 and/or Smad3 as they exist naturally because the claims do not particularly point out any non-naturally occurring differences between the claimed products and the naturally occurring products. In the absence of the hand of man, the naturally occurring products are considered non-statutory subject matter. *See Diamond v. Chakrabarty*, 447 U.S. 303, 206 USPQ 193 (1980). In order to obviate the instant

rejection, the Examiner suggests that the claims should be amended to indicate the hand of the inventor, e.g., by insertion of "isolated" or "purified" provided the support for such an amendment can be identified in the specification as originally filed. See MPEP 2105.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

14. Claim 4 recites the limitation of "the mammal is a rabbit" for the polyclonal antibody according to any one of claims 1 to 3. There is insufficient antecedent basis for this limitation in the claim.

15. Claim 5 recites the limitation of "the raised antiserum" for the polyclonal antibody according to any one of claims 1 to 3. There is insufficient antecedent basis for this limitation in the claim.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

16. Claims 1, 2, 4, and 5 are rejected under 35 U.S.C. 102(a) as being anticipated by Furukawa et al. (Hepatology, September 27, 2003, 38:879-889, for date see Appendix 1).

The claims are drawn to 1. Polyclonal antibody specific for a phosphorylated linker region in Smad2 and/or Smad3; 2. The polyclonal antibody according to claim 1, obtained from antiserum raised by immunizing a mammal with a phosphorylated product of a peptide including an amino acid sequence in the linker region of Smad2 or Smad3; 4. The polyclonal antibody

according to anyone of claims 1 to 3, wherein the mammal is a rabbit; 5. The polyclonal antibody according to any one of claims 1 to 3, wherein the raised antiserum is affinity purified with a phosphorylated peptide(s).

Furukawa et al. teach the production of polyclonal antibodies to the phosphorylated linker region of Smad3 that was raised against a synthetic peptide from the linker region (amino acids 201-214) that was phosphorylated at serine positions 207 and 212, see p. 880, right column and Fig. 2. Furukawa et al. teach that the polyclonal antibodies were affinity purified with said phosphorylated peptides, see p. 880, right column.

Claims 2, 4, and 5 are product by process claims, thus regardless of process of making the antibody, the prior art antibody functions in the same manner as the claimed antibody and the patentability of a product-by-process claim is determined by the novelty and nonobviousness of the claimed product itself without consideration of the process for making it which is recited in the claim. In re Thorpe, 227 USPQ 964 (Fed. Cir. 1985).

Claim Rejections - 35 USC § 103

17. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

18. Claims 1-5 are rejected under 35 U.S.C. 103(a) as being unpatentable over by Kretzschmar et al. (Genes & Development, 1999, 13:804-816, IDS item), in view Harlow and Lane (Antibodies, a Laboratory Manual, Cold Spring Harbor Laboratory Press, 1988, p. 93-94 and p.142).

The claims are drawn to 1. Polyclonal antibody specific for a phosphorylated linker region in Smad2 and/or Smad3; 2. The polyclonal antibody according to claim 1, obtained from

antiserum raised by immunizing a mammal with a phosphorylated product of a peptide including an amino acid sequence in the linker region of Smad2 or Smad3; 3. The polyclonal antibody according to claim 2, wherein the phosphorylated product of a peptide including the amino acid sequence in the linker region of Smad2 for the immunization is: Pro Ala Glu Leu p-Ser Pro Thr Thr Leu p-Ser Pro Val Asn His Ser (SEQ ID NO: 1) wherein p-Ser represents phosphorylated serine and the phosphorylated product of a peptide including the amino acid sequence of the linker region of Smad3 for the immunization is: Ala Gly Ser Pro Asn Leu p-Ser Pro Asn Pro Met p-Ser Pro Ala (SEQ ID NO 2) wherein p-Ser represents phosphorylated serine; 4. The polyclonal antibody according to anyone of claims 1 to 3, wherein the mammal is a rabbit; 5. The polyclonal antibody according to any one of claims 1 to 3, wherein the raised antiserum is affinity purified with a phosphorylated peptide(s).

Claims 2, 4, and 5 are product by process claims, thus regardless of process of making the antibody, the prior art antibody functions in the same manner as the claimed antibody and the patentability of a product-by-process claim is determined by the novelty and nonobviousness of the claimed product itself without consideration of the process for making it which is recited in the claim. In re Thorpe, 227 USPQ 964 (Fed. Cir. 1985).

Kretzschmar et al. teach an isolated recombinant Smad2 and Smad3 that are directly phosphorylated in the linker region by Erk 2 and these phosphorylations are stimulated by Epidermal Growth Factor and the activated oncogene RasV12, see p. 807-right column, p. 808-left column, and Fig. 5. Kretzschmar et al. teach that Ras induced phosphorylation of Smad2 and Smad3 in the linker region inhibits the nuclear accumulation of the Smads and their ability to

mediate Transforming Growth Factor Beta antiproliferative responses in cancer cells, see p.810, right column and Abstract.

Kretzschmar et al teach as set forth above, but do not teach polyclonal, rabbit antibodies to the phosphorylated linker region in Smad2 and/or Smad 3.

Harlow and Lane teach the five most commonly used laboratory animals for the production of antisera are mice, rats, hamster, and guinea pigs, see p. 93 and Table 5.2. Harlow and Lane further teach that rabbits represent a good choice for the routine production of polyclonal antibodies because they are easy to keep and handle, can be safely and repeatedly bled, and the antibodies they produce are well characterized and easily purified, see p.92 and Table 5.2.

Additionally, Harlow and Lane teach that, although in theory monoclonal antibodies can be used for all of the tasks for which polyclonal antibodies are used, in practice one cannot predict how a monoclonal antibody will function, see p. 142, first para., and Table 6.1. Further, Harlow and Lane teach that ". . . producing exactly the right set of monoclonal antibodies is often a difficult and laborious job,." (p. 142, first para).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have produced antibodies to the well known phosphorylated SMAD2 and/or 3 because the Board of Patent Appeals and interferences has taken the position that once an antigen has been isolated, the manufacture of antibodies, which include polyclonal antibodies against it is *prima facie* obvious. See Ex parte Ehrlich, 3 USPQ 2d 1011 (PTO Bd. Pat. APP. & Int. 1987), Ex parte Sugimoto, 14 USPQ 2d 1312 (PTO Bd. Pat. App. & Int. 1990). Further, it would have been prima facie obvious and one would have been motivated to produce polyclonal

antibodies to the well known phosphorylatedSMAD2 and/or 3 because Harlow et al specifically teach that monoclonal antibodies are often more time-consuming and costly to prepare and they are not necessarily the best choice for certain immunochemical techniques. Although in theory, monoclonal antibodies can be used for all of the tasks that require or benefit from the use of polyclonal antibodies, in practice, producing exactly the right set of monoclonal antibodies is often a difficult and laborious job and polyclonal antibodies are useful for cell staining, immunoprecipitation and immunoblot techniques. Given the conventional nature of the production of polyclonal antibodies at the time the invention was made, one would have had a reasonable expectation of successfully producing antibodies to phosphorylated SMAD2 and/or 3

One would have been motivated to make antibodies to the phosphorylated SMAD2 and/or 3because Kretzschmar et al. shows the proteins in two different phosphorylation states and it would be useful to have antibodies that differentiate between phosphorylated and unphosphorylated SMAD2 and/or 3. Further, it would have been expected that at least a subset of the polyclonal antibodies produced would be specific for a phosphorylated linker region of either SMAD2 and/or 3.

Furthermore, the prior art teaches that mammals are routinely used for antibody production and rabbits have numerous advantages for the production of polyclonal antibodies. Thus one of ordinary skill in the art would have had motivation and a reasonable expectation of success in making and using the claimed invention for the reasons above.

19. If applicant disagrees with any rejection set forth in this office action based on examiner's establishment of a priority date April 13, 2004 for the instantly claimed application serial number

10/822,860, applicant is invited to submit evidence pointing to the serial number, page and line where support can be found establishing an earlier priority date.

20. No claims are allowed.

21. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Peter J. Reddig whose telephone number is (571) 272-9031. The examiner can normally be reached on M-F 8:30 a.m.-5:00 p.m..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shanon Foley can be reached on (571) 272-0898. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Peter J. Reddig, Ph.D.
Examiner
Art Unit 1642

SUSAN UNGAR, PH.D
PRIMARY EXAMINER

PJR